provided that they never result in a complete loss of function. Recent experiments (Alexander et al. 2009. 10.1073/pnas.0906408106) have shown that it is possible to induce a switch in global protein fold by point mutations, lending some support to this conjecture. However, the relation between structure and function remains unclear, due to the possibility of binding-induced fold switching. In this study, we use a coarse grained, continuous model to explore sequence-structure space between two elementary folds: an alpha-helix and a beta-hairpin. Furthermore we assess functionality by performing binding simulations to two different targets, each of which is a natural partner to one of the two folds. We identify a mutational pathway that features a sharp switch between the folds. Despite this sharpness, binding-induced fold switching occurs for intermediate sequences, so that the switch in fold does not coincide with the switch in function. The underlying evolutionary potential changes gradually in contrast to the abrupt change in fold. This work furthers our understanding of the structure-function relationship and how new functions might arise along a mutational pathway between two structures.

2213-Plat
Hydophobic Guided Protein Folding
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Protein folding simulations have the potential to help us figure out the problem of protein folding. However, the highly frustrated energy landscapes of protein folding limits the use of these techniques. Hence, many new algorithms are developed each year aiming at improving sampling efficiency, producing results in shorter times. We have developed and tested an algorithm using GPU technology that allows us to fold several proteins within weeks of computational usage. Our work extends on the principles of protein folding through zipping and assembly. In this view, local events such as helix formation happen first (zipping), and non-local ones later (assembly). The assembly step is slow: in order to form native like contacts the residues involved have to first find each other. Our algorithm takes advantage of the fact that proteins form hydrophobic cores to guide the assembly step. We accelerate the process by adding restraints in our simulations that brings pairs of hydrophobic residues together, favoring the formation of native-like contacts. Since not all hydrophobic pairs will lead to native-like contacts we use a Hamiltonian and Temperature Replica exchange algorithm (H,T-REMD), that allows us to modulate the strengths of these restraints. Thus, the restraints that the underlying molecular force field favors are enforced, where as the ones that are not favored are turned off.
This method allows us to jump between different sets of contacts easily, sampling many different topologies and limiting the amount of sampling that is required in between. In this way we have been able to get native-like structures for a small set of proteins. During my presentation I will show how the method works and how successful it is in a small set of proteins.

2214-Plat
Exact Partition Function Zeros of the Wako-Saitô-Muñoz-Eaton Protein Model
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Protein is an intrinsically finite size system with heterogeneous components, which is in contrast to infinite-size homogeneous systems studied in traditional statistical physics, and it is of interest to see to what extent methodologies of statistical physics can be used for studying protein folding. Partition function zeros(PFZs) method is a tool used in statistical physics for studying phase transition, where instead of computing quantities in real temperature, the zeros of the partition function in the complex temperature plane are examined. In this work, I show that the PFZs method can be used for distinguishing two-state and barrierless downhill folding transitions, by computing exact partition function zeros of the Wako-Saitô-Muñoz-Eaton protein model. I compute the PFZs for various secondary structural elements, and for two proteins 1BBL and 1I6C, which exhibit features that clearly distinguish distinct types of folding transitions. The result is expected to form basis for further application of the method to finite heterogeneous systems.
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2215-Plat
Allosteric Coupling via Communication of Distal Disorder-To-Order Transitions
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Disorder-to-order transitions in proteins can play critical roles in regulating function. Corepressor bio-5'-AMP binding to the E. coli biotin repressor promotes homodimerization that is a prerequisite to sequence-specific DNA binding and resulting transcription repression. Folding of a loop segment comprised of residues 211-222 in the corepressor binding site is required to obtain the full −4.0 kcal/mole energetic coupling between bio-5'-AMP binding and dimerization. Several additional loops, some of which are disordered in the unliganded monomer but folded in the liganded dimer, participate directly in the homodimer interface. Alanine scanning mutagenesis has demonstrated the functional significance of these loops for dimerization. Replacement of a glycine at position 142 in loop 140-146 with alanine results in complete abolition of coupling of corepressor binding to dimerization. Consistent with solution measurements and in contrast to wild type BirA, the structure of this variant solved by x-ray crystallography reveals a monomeric liganded protein. Moreover, the alanine replacement results in adoption of an alternative conformation by the 140-146 loop. Furthermore, distinct from wild type corepressor-bound BirA, both a neighboring dimer interface loop comprised of residues 193-199 and the 211-222 loop that is located 33 Å away from the alanine replacement are disordered in the liganded variant. These results support a model for energetic coupling between ligand binding and dimerization in which distant disorder-to-order transitions are communicated through the folded protein core.

2216-Plat
Reshaping Antibody Diversity
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Some species mount a robust antibody response despite having limited genome-encoded combinatorial diversity potential. Cows are unusual in having exceptionally long CDR H3 loops and few V regions, but the mechanism for creating diversity is not understood. Deep sequencing reveals that ultralong CDR H3s contain a remarkable complexity of cysteines, suggesting that disulfide-bonded minidomains may arise during repertoire development. Indeed, crystal structures of two cow antibodies reveal that these CDR H3s form a very unusual architecture composed of a β strand ''stalk'' that supports a structurally diverse, disulfide-bonded ''knob'' domain. Diversity arises from somatic hypermutation of an ultralong DH with a severe codon bias toward mutation to cysteine. These unusual antibodies can be elicited to recognize defined antigens through the knob domain. Thus, the bovine immune system produces an antibody repertoire composed of ultralong CDR H3s that fold into a diversity of minidomains generated through combinations of somatically generated disulfides.
Wang and Ekiert, et al. Cell (2013) 153:1379-93.

2217-Plat
Computing Conformational Entropy in Antibody Interfaces
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Loss of conformational entropy is crucial in protein-protein binding affinity, including antibody-antigen affinity. Computational protein design methods, however, often only account for the enthalpy of binding when optimizing antibody interfaces. These methods ignore conformational entropy because accounting for entropy is expensive: all the conformational states of the unbound and bound states contribute to conformational entropy. Even in a simplified model, where only the conformational states of the interfaces are evaluated, the number of states grows exponentially with the size of the interface. This makes counting the states of the interface impossible for average-sized antibody-antigen interfaces. We have developed a hybrid probabilistic/deterministic method to compute the binding affinity (the K* score [1], which approximates the association constant Ka) of large protein interfaces that antibodies share with antigens. The algorithm uses a probabilistic randomized method to provably find a lower bound on the partition function for the bound and unbound complexes, and a deterministic algorithm to find a provable upper bound on each of the partition functions. After sufficient iterations, both methods converge. However, only a few iterations are necessary to provide bounds that are tight enough to rank sequences on protein-protein interfaces. We apply this algorithm to rank sequences of the broadly neutralizing human anti-HIV-1 antibody NIH45-46 [2] by their K* score and compare against methods that only consider a single structure.
[1] Georgiev, Ivelin, Ryan H. Lilien, and Bruce R. Donald. ''The minimized dead-end elimination criterion and its application to protein redesign in a hybrid scoring and search algorithm for computing partition functions over molecular ensembles.'' Journal of Computational Chemistry 29.10 (2008): 1527-1542.
[2] Scheid, Johannes F., et al. ''Sequence and structural convergence of broad and potent HIV antibodies that mimic CD4 binding.'' Science 333.6049 (2011): 1633-1637.